

TITLE: A Randomized Control Trial of Buprenorphine vs Buprenorphine/naloxone on the Effects of Maternal Symptomatology

OBJECTIVE: To compare buprenorphine and buprenorphine/naloxone on suppressing maternal opiate withdrawal symptoms

BACKGROUND:

Opioid use has been on the rise throughout the United States and particularly among reproductive age women. Amongst pregnant women ages 15-44 years old, 5.4% admitted to currently using illicit drugs with the highest rate occurring in the first trimester. (Bastian 2017) Opioid use disorders in pregnancy has known adverse social, economic, legal and health effects on both the mother and developing fetus. (ACOG 2017) The use of opioids in pregnancy continue to be a trending topic amongst various multidisciplinary medical and research committees. The use of opioids in pregnancy has been associated with many adverse pregnancy outcomes including neonatal abstinence syndrome, prolonged hospital stays, intrauterine growth restriction, and fetal demise. (ACOG 2017, Jones 2010) Inadequately treated opioid disorders can also lead to maternal withdrawal symptoms, increased cravings, at risk behaviors, infectious diseases, and other illicit substance usage (ACOG 2017) Research endeavors continue to focus and explore the optimal treatment regimens to prevent and decrease some of the known maternal and newborn adverse outcomes. (Bastian 2017, Caritis 2017) Recent studies have found that increasing the dosing frequencies of buprenorphine is more efficacious to prevent maternal withdrawal symptoms, improve compliance, and theoretically produce better pregnancy outcomes. For example, when patients were given the option to choose their dosing frequencies, most patients (45%) elected for three times a day dosing compared to once or twice a day to minimize cravings and withdrawals. (Caritis 2017)

Over the past few decades, investigators and clinicians have contemplated the first line treatment for various opioid use disorders (methadone vs. buprenorphine). According to a recent 2017 executive summary endorsed by the Eunice Kennedy Shriver National Institute of Child Health and Human Development, Centers for Disease Control and Prevention, and various medical specialty governing organizations there has been a shift in the maintenance and treatment for opioid use disorders in pregnant women from methadone to buprenorphine, a partial mu opioid agonist. (Mendelson 2003) Buprenorphine has many preferential characteristics over methadone including decreased risk of maternal overdose, lower incidence of preterm labor, less frequent clinical visits, shorter duration of neonatal hospital stay and treatment for neonatal abstinence syndrome. (ACOG 2017, Jones 2010, Caritis 2017, Mendelson 2003)

Buprenorphine/naloxone, a combination opioid of buprenorphine and naloxone, has also been investigated as an alternative to treatment and maintenance for opioid use disorders. The advantage of the combination of buprenorphine with naloxone is that it reduces the potential for abuse. As a partial mu opioid agonist, buprenorphine alone has the capacity to induce typical opioid effects such as euphoria, which are enhanced when the drug is taken intravenously. By combining buprenorphine with naloxone, an opioid antagonist, the capacity for buprenorphine to be abused is reduced. In Finland, where buprenorphine was the most abused opioid, patients

were transferred to buprenorphine/naloxone to reduced abuse potential. (Smojoki 2008) In non-pregnant patients, Fudela et al described that both buprenorphine/naloxone in combination and buprenorphine alone are safe and reduce the use of opiates and the craving for opiates among opiate-addicted persons in an office-based setting. (Fudela 2003) Oral naloxone remains essentially inert unless the medication is heated for possible intravenous use and when naloxone is taken orally it is not detected in the blood, and with sublingual use systemic levels are low. (Lund 2013, Geber 1975, Poon 2014)

There is not a lot of safety data for the use of buprenorphine/naloxone use in pregnancy. The FDA has classified buprenorphine/naloxone as Category C, which means that animal studies have suggested adverse effects on the fetus; although these adverse effects are observed at doses higher than those recommended for humans. There is relatively little data from humans. One small study (N=10) compared fetal outcomes including gestational age, 1 and 5-minute Apgar scores, head circumference, length and weight at birth, treatment for NAS, and length of hospital stay for NAS and concluded that there were no obvious differences in neonatal outcomes related to the use of buprenorphine/naloxone compared to buprenorphine alone. (Smojoki 2008) Nguyen et al evaluated 26 mother infant dyads in comprehensive medication-assisted treatment with buprenorphine and naloxone during pregnancy and found buprenorphine/naloxone shows relative safety in pregnancy. (Nguyen 2017) In 2014, a retrospective appraisal of 58 infants whose mothers were treated with buprenorphine/naloxone and 92 infants whose mothers were treated with methadone demonstrated no apparent significant adverse neonatal outcomes following treatment with either maintenance medication. (Gawronski 2014) Jumah et al assessed 855 mother infant dyads with 62 women taking buprenorphine/naloxone in pregnancy, 159 women taking other opioids and 618 women with no opioid exposure. (Jumah 2016) They reported no significant differences in birthweight, preterm delivery, congenital abnormalities, Apgar scores, rates of caesarean sections or stillbirths for infants from the buprenorphine/naloxone group compared to those taking no opioids. (Jumah 2016) Thus, although there are no large-scale, systematic investigations of buprenorphine/naloxone on fetal outcomes, the data do not suggest a degree of risk that would preclude the proposed study.

Reports of maternal symptomatology often employs the use of a subjective reporting and objective questionnaires, most notably the Clinical Opioid Withdrawal Scale (COWS). (Bastian 2017, ACOG 2017, Jones 2010) The use of various questionnaires and self-reporting are vital to health care providers detecting inadequate treatment and making any necessary changes to optimize treatment protocols for the patient, such as changing medication dosages or frequencies of administration. Strain et al has shown that buprenorphine/naloxone films reduce Clinical Opioid Withdrawal Scale (COWS) and the film is an acceptable delivery system. (Strain 2012)

Clinically, we use both buprenorphine and buprenorphine/naloxone, but we would like to conduct this more systematic study of the safety and efficacy of buprenorphine and buprenorphine/naloxone in opioid dependent pregnant women. We propose a randomized control trial in which either buprenorphine or buprenorphine/naloxone will be prescribed to a cohort of pregnant women seeking medication-assisted treatment for opioid use disorders.

Primary Outcome: To compare compliance with buprenorphine versus buprenorphine/naloxone medication-assisted treatment (MAT) in pregnant women. Compliance will include the incidence of urine toxicology testing positive for illicit substances at the time of admission for delivery and the percentage of women that need a significant dosing change (>50% increase or decrease) in maintenance medication throughout antenatal care.

Secondary Outcomes:

Maternal outcomes including: mode of delivery, patient satisfaction, maternal relapse, prenatal COWS score, drug cravings score, dosing frequency, diversion rates, serum levels of metabolites of buprenorphine (norbuprenorphine, buprenorphine glucuronide, and norbuprenorphine glucuronide), change in frequency of daily dosing (i.e. daily, twice a day, three times a day, or four times a day), and placenta histology.

Newborn outcomes including: Neonatal Abstinence Syndrome (NAS) rate, duration of newborn inpatient hospital stay, need and duration of neonatal morphine therapy, gestational age at birth, birth weight, need for NICU admission (not typical at Stony Brook for these babies – usually go to newborn nursery)

RESEARCH DESIGN & METHODS:

The inclusion/exclusion criteria are as follows:

Included in the study will be pregnant women of any gestational age:

- 18 years of age and older
- With a confirmed viable intrauterine pregnancy
- Opioid Use Disorder
- Care in a Stony Brook Medicine OBGYN clinical office sites
- Medication-assisted treatment through Stony Brook Medicine OBGYN office sites

Excluded from the proposed study will be those:

- Known or suspected allergy to buprenorphine or buprenorphine/naloxone
- Carrying a fetus with known aneuploidy or anomaly

Women will be recruited in one of three ways:

1. Stony Brook Medicine Obstetrics and Gynecology outpatient clinic sites during their initial or routine prenatal visits
2. Pregnant patients admitted to the Stony Brook University Hospital with opioid withdrawal

Women will be recruited from Stony Brook Medicine's Obstetrics and Gynecology Outpatient clinic sites during their routine prenatal visits. Women who agree to participate in the study will be consented and randomized. Women will be randomly assigned to receive buprenorphine or buprenorphine/naloxone and dosing decided by her trained authorized (has DEA waiver) prescribing obstetric provider. The randomization scheme will be generated by using the website randomization.com (<http://www.randomization.com/> last accessed June 23 2018). The drug regimen will be initiated during the first encounter, which can occur at any gestational age in the pregnancy. The respective medication assigned will be started at the lowest dosage possible to

achieve a therapeutic effect that is based on the patients' symptomatology, drug craving/COWS questionnaires, and provider's evaluation. This process is no different from those not participating in this study. The regimen for increasing the patient's medication will be determined at each prenatal/post-partum visit by the patient's subjective symptomatology, drug craving/COW questionnaires, and provider's evaluation. The subjects will continue the respective medication and be monitored routinely during the pregnancy and up to 6 weeks post-partum, depending on the patient's needs and the provider's clinical assessment. Pain management for labor and post delivery are determined if additional opioids are needed, it is decided in conjunction with OB provider and anesthesia providers. There is no contraindication to short courses of opioids for operative pain management in women using buprenorphine.

Each patient will be evaluated using the Clinical Opioid Withdrawal Scale (COWS) by the provider and complete a drug cravings questionnaire prior to prescribing the initial medication-assisted treatment. (attachments) The 'Brief Substance Cravings scale' and 'COWS' questionnaire' are standardized validated tools for screening opioid and substance abuse patients. The questionnaires will be performed at each prenatal care visit throughout the gestation to determine any medication dosage changes that may be necessary. Withdrawing or de-escalating of medication-assisted treatment during pregnancy is not recommended in pregnancy, but not contraindicated. In well-motivated, select patients this may occasionally be attempted. As part of routine care and prescribing buprenorphine or buprenorphine/naloxone, the University Associates in Obstetrics and Gynecology buprenorphine treatment agreement / contract must be signed (a usual requirement of medication-assisted treatment). This agreement informs women that they will be routinely have urine drug toxicology analysis performed to confirm compliance with opioid maintenance therapy. (attachment)

Dosing of the buprenorphine or buprenorphine/naloxone is based on clinical history and maternal symptoms. The COWS scoring allows for standardization of a degree of opioid withdraw.

Initial dosing	Clinical
Buprenorphine 2 mg to 8 mg daily	Light to moderate history of opioid use (heroin, oxycodone, etc.) and/or COWS scores 5-24
Buprenorphine 8 mg to 16 mg daily	Heavy history of opioid use (heroin, oxycodone, etc.) and/or COWS scores 25-36+
Buprenorphine/naloxone 4 mg/1 mg daily once daily or BID	Light to moderate history of opioid use (heroin, oxycodone, etc.) and/or COWS scores 5-24
Buprenorphine/naloxone 8 mg/2 mg daily once daily or BID	Heavy history of opioid use (heroin, oxycodone, etc.) and/or COWS scores 25-36+

Follow-up modification of the dosing is based on maternal response and symptoms (COWS)

Women who are non-compliant with their prescribed medications will be managed in the same manner as if they were not participating in this study. We attempt to contact the women when

they do not arrive for their scheduled visit. We determine what events precipitated the return to unhealthy behavior. The women are counseled, evaluated for possible inpatient management, support systems assessed, and medication-assisted treatment may require dosage changes. All women are encouraged to return for care without judgement.

A maternal blood sample of approximately 5ml will be collected by venipuncture at the time of admission to the hospital for delivery, which will be obtained at the same time as her routine admission labs. An umbilical cord blood sample will be collected after delivery of the neonate at the same time other routine umbilical cord labs are obtained. These blood and serum samples will be used to detect metabolites of buprenorphine (norbuprenorphine, norbuprenorphine glucuronide, buprenorphine glucuronide) and correlate their level with known adequate levels in pregnancy. (Bastian 2017, Caritis 2017) The placenta will be sent to pathology as per the usual protocol in opioid use disorders for gross pathological and histological assessment. Women will also be asked to complete a maternal demographics form and drug use questionnaire after her delivery.

All maternal serum samples and cord blood specimens will be coded with a case number that will be linked to the participant. All specimens will be stored at -80°C until analysis at the completion of the study via high performance liquid chromatography with tandem mass spectrometry.

Outpatient visit details, delivery characteristics, and maternal and neonatal outcomes will be collected from Stony Brook University Hospital's electronic medical record. The collection of mother and neonatal data will be completed simultaneously. To ensure privacy, all data will be coded with a case number.

An independent Data Safety Monitoring Board (DSMB) will include reviews every 6 months after enrollment begins and recur every 6 months thereafter, evaluating adverse outcomes. The Data Safety Monitoring Board will include the following persons: (Department of Psychiatry and Addiction Medicine specialist) (Pediatrics Nurse Practitioner and Addiction Specialist), and (Department of Anesthesiology and Pain Medicine Specialist).

The following data will be collected:

Demographics:

Maternal: age, gravidity, parity, GA at time seeking treatment for withdrawal, admitted to hospital (yes/no), drug history (heroin, oxycodone, buprenorphine, fentanyl, others), length of drug abuse (number of months and/or years), COWS score, drug cravings scale score, randomized group: Buprenorphine or Buprenorphine/naloxone, opioid maintenance dosage at induction, dosage frequency, dosage increase (yes/no, amount), dosage decrease (yes/no, amount), living situation (have a place to live/homeless), who living with (family, significant other, friend), working or not, psychiatric history (anxiety, depression, bipolar, personality disorder, other), receiving prenatal care (yes/no, number of prenatal visits before delivering (<4, 5-9, 10-14) , medical problems (yes, no), comorbidities of drug use (cellulitis/endocarditis), infectious disease (hepatitis/hepatitis C/HIV), history of admission to a rehab facility (yes/no),

history of opioid maintenance medications (yes/no), tobacco use, sexually transmitted disease in pregnancy (yes/no)

Delivery: year of delivery, GA at delivery, meconium at rupture of membranes, mode of delivery (vaginal, cesarean, assisted delivery (vacuum or forceps), pain medication in labor (IV pain meds, epidural)

Fetal: fetal anomaly (yes/no), APGAR 1 minute (<4, 4-7, 8-9), APGAR 5 minutes (<4, 4-7, 8-9), pH of cord blood gas (<7, 7-7.2, >7.2), cord blood gas base excess (<12, >12), birth weight (<2500g, 2501 g-3000g, 3000g-3500g, >4000g), NICU admission (yes/no), days in hospital, received morphine (yes/no), Neonatal Abstinence Syndrome (yes/no)

Specimens: Cord blood buprenorphine, maternal plasma buprenorphine glucuronide, norbuprenorphine, and norbuprenorphine glucuronide

SAFETY: All study participants randomized to receiving buprenorphine or buprenorphine/naloxone will be monitored for medication compliance, withdrawal symptoms, cravings, and other illicit drug use at each routine prenatal care visit as per the usual standard (monitored as if they were not part of a study). According to Debelak et al, the use of buprenorphine/naloxone supplementation found no obvious significant adverse maternal or neonatal outcomes. (Debelak 2013, Simojoki 2008) According to Wiegand and colleagues, a cohort study of 31 pregnant patients treated with naloxone and buprenorphine compared to methadone, the neonates exposed in utero to buprenorphine/naloxone exhibited less frequent neonatal abstinence syndrome (25.1% compared to 51.6% for methadone) and shorter hospitalizations. (Wiegand 2015) Jumah et al also described that there likely is no harm from taking buprenorphine/naloxone opioid agonist treatment in pregnancy. (Jumah 2016)

Part of routine obstetrical care for women on medication assisted treatment, prescribed buprenorphine or buprenorphine/naloxone, is close evaluation with ultrasound of fetal growth throughout the pregnancy. In addition, these women undergo fetal testing weekly from 34 weeks until delivery; to provide reassurance that the fetus is doing well and prevent stillbirth. This monitoring is the same for those not participating in this study.

Specifically addressing safety issue for the participants is as follows:

- You and your baby will be exposed to buprenorphine (Subutex) or buprenorphine/naloxone (Suboxone). Studies suggest that both buprenorphine and buprenorphine/naloxone use in pregnancy are safe; however, risks to the fetus and developing child are not completely known. We will be monitoring your urine for other drug use as we would do in all pregnancies we treat with buprenorphine.
- Your baby short-term effects from the medications may include developing withdrawal at birth and/or the first week of life. No clear long-term effects in the fetus have been identified from medication-assisted treatment with buprenorphine or buprenorphine/naloxone; however, risks to the developing child are not completely known. Based on other opioid medications, normal development is anticipated.
- Some women may occasionally experience withdrawal symptoms and drug cravings during this study as medications are being adjusted to ideal levels as per the usual protocol in

women we treat with buprenorphine. Maternal withdrawal symptoms in pregnancy can also lead to withdrawal symptoms for your baby.

- Rarely some women may experience discomfort at the time of the blood draw. This may include temporary pain and bruising where the needle enters the skin, and sometimes, fainting and/or infection.
- There is a risk of allergic reaction to the buprenorphine or buprenorphine/naloxone
- Other common maternal adverse reactions include nausea, vomiting, diarrhea, headache, constipation, insomnia, rhinitis, and diarrhea.
- Since this is a research study, not all risks may be known at this time; there may be unforeseen risks associated with study participation

STATISTICAL ANALYSIS PLAN: Data collected from this study will be analyzed with SPSS statistics software package. Student t tests will be performed for continuous variables and Chi-Square test/odds ratios for categorical variables. Multivariate logistic regression will be performed on selected maternal and neonatal outcomes. We assumed a baseline incidence of urine toxicology testing negative for illicit substances at the time of admission for delivery for compliant women will be 70-80% compared with non-compliant women where we anticipate a urine toxicology negative in 35-40% (Chaven 2017) Based on this, 66 women in each group would be enrolled with a power of 0.80 and an alpha of 0.05 to detect a statistically significant difference. To account for the possibility of up to a 10% drop out or loss to follow-up, the target enrollment of 72 for each of the groups is projected. A p value < 0.05 will be considered statistically significant.

FUNDING STATUS, DETAILS: The current study will be funded by internal funds from the Department of Obstetrics, Gynecology, and Reproductive Medicine.

HUMAN SUBJECTS RESEARCH PROTECTION FROM RISK

Risk to subjects: Minimal

Adequacy of Protection Against Risks: This randomized control trial poses greater than minimal risks to the participants and their neonates. According to Debelak colleagues, the use of buprenorphine/naloxone supplementation found no obvious significant adverse maternal or neonatal outcomes. (Debelak 2013) According to Wiegand et al, a cohort study of 31 pregnant patients treated with buprenorphine/naloxone and compared to methadone, neonates exposed in utero to naloxone and buprenorphine exhibited less frequent neonatal abstinence syndrome (25.1% compared to 51.6% for methadone) and shorter hospitalizations. (Weigand 2015, Chavan 2017)

In regards to the participants and neonates' health information, care will be taken to ensure privacy. All data and specimens will be coded with a case number, and exported to a REDcap application system. The REDcap application data will be kept on the department's shared hard drive, found only on password-protected computers, located on the university grounds in locked offices.

Importance of Knowledge to be Gained: The current study would assess the efficacy and compliance of buprenorphine/naloxone vs buprenorphine in pregnant women.

Potential Benefits of Proposed Research to Subjects and Others:

The current study will be a randomized control trial to assess the efficacy of buprenorphine/naloxone vs buprenorphine on maternal withdrawal symptoms and drug cravings. The study will also provide information on the role of buprenorphine/naloxone and buprenorphine on various maternal and neonatal outcomes.

Results of this study will provide obstetricians and other opioid maintenance treatment providers with a means of improved management of maternal withdrawal, cravings, and opioid abuse if a beneficial association with buprenorphine/naloxone use is found while reducing the possible potential for abuse from formulations of buprenorphine alone.

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